In claim 17, line 6, please delete "antagonist".

## REMARKS

**Formality matters**

The instant application claims priority to a case originally filed as USSN 08/589,982 on January 23, 1996. Applicants filed a petition to convert this earlier case to a provisional application January 14, 1997. However, the Patent Office has not assigned a provisional application serial number yet. Therefore, Applicants are unable to update the "Related Application" paragraph on page 1 of the instant application at this stage.

Applicants seek to defer filing formal drawings until allowance.

A SEQ ID No. has been assigned for the light chain of the full length IgG2 huH52 on page 13, lines 9-12 (see page 12, lines 27-31). Reconsideration of the objection is respectfully requested.

**§112, first paragraph**

The Examiner has said that the enablement requirements of 35 USC §112, first paragraph may be satisfied by a deposit of the hybridoma which produces the antibody of claims 11-12. Claim 11 now refers to SEQ ID NO's 10 and 11 and Applicants respectfully submit that this claim (and claim 12 which depends thereon) is enabled by the specification. Applicants submit that the H52 hybridoma does not need to be deposited to satisfy Section 112.

Claim 13 is rejected under 35 USC §112, first paragraph. Applicants submit that this claim is enabled. Nevertheless, in order to expedite prosecution and without acquiescing in the rejection, this claim has been cancelled.

Applicants respectfully request that the Section 112, first paragraph rejections be reconsidered and withdrawn.

**§112, second paragraph**

Claims 11-13 and 15-17 are rejected under 35 USC §112, second paragraph as allegedly being indefinite.

A. The amendment of claim 11 (on which claim 12 depends) to refer to SEQ ID NO's as suggested

by the Examiner obviates this rejection.

B. The rejection of claim 13 is moot due to the nonprejudicial cancellation of this claim.

C. Claim 15 (on which claim 16 depends) and claim 17 have been amended by removal of the offending word "antagonist".

D. As suggested by the Examiner, claim 10 now recites --minutes--.

Reconsideration of the Section 112, second paragraph rejections is respectfully requested in view of the above.

**§102(b) - Mori *et al.***

Claims 1-2 and 6-10 are rejected under 35 USC §102(b) as being anticipated by Mori *et al. Stroke* 23(5):712-718 (1992). Mori *et al.* is cited for teaching inhibiting focal cerebral ischemia in baboons with anti-CD18 antibody 1B4.

Mori *et al.* occluded the right middle cerebral artery (MCA) of the baboon by inflating an extrinsic MCA balloon to 100µl. This "arterial obstruction" was removed by deflating the balloon following administration of the antibody (last paragraph of the first column on page 713). Claim 1 of the present application relates to a method for treating focal ischemic stroke wherein cerebral blood flow is increased or infarct size is reduced upon administration of an effective amount of an anti-CD18 antibody <u>in the absence of removal of the arterial obstruction</u>. Since Mori *et al.* removed the arterial obstruction, Applicants submit that the pending claims are novel over this reference. Withdrawal of the rejection is respectfully requested.

**§102(b) - Clark *et al.***

Claims 1-2 and 6-10 are rejected under 35 USC §102(b) as being anticipated by Clark *et al. Stroke* 22(7):877-883 (1991). Clark *et al.* is relied upon as teaching reducing central nervous system ischemic injury in rabbits with anti-CD18 antibodies.

Clark *et al.* evaluated both a reperfusion model (*i.e.*, one in which the arterial obstruction was removed) and an irreversible microemboli model (*i.e.*, where the arterial obstruction was not removed). For the reperfusion model, they placed a snare ligature occluding device around the abdominal aorta just below the left renal artery. To induce ischemia, they tightened and clamped

the occluder. Then they removed the arterial obstruction by unclamping and removing the snare ligature. See column 1 paragraph 1 on page 878 of Clark *et al.* In the irreversible model, microspheres were injected through a lateral neck incision (last paragraph in column 1 on page 878). Clark *et al.* found that treatment with anti-CD18 antibody reduced CNS ischemic injury in the reperfusion model, but not in the irreversible occlusion model (last paragraph on page 882). Thus, Clark *et al.* teaches away from the instantly claimed invention by indicating that anti-CD18 antibodies will provide no clinical benefit in focal ischemic stroke where the arterial obstruction is not removed. Withdrawal of the rejection is respectfully requested.

**§102(a) - Bednar *et al.***

Claims 1-2 and 6-10 are rejected under 35 USC §102(a) as being anticipated by Bednar *et al. Neurol. Res.* 18:171-175 (1996). This is not prior art, being published April 1996, whereas the instant claims enjoy the priority of the earlier application filed January 23, 1996. Reconsideration of the rejection is respectfully requested.

**§103 - Mori *et al.* or Clark *et al.* or Bednar *et al.* or Lindsberg *et al.***

Claims are rejected under 35 USC §103 as being unpatentable over Mori *et al. Stroke* 23(5):712-718 (1992) or Clark *et al. Stroke* 22(7):877-883 (1991) or Bednar *et al. Neurol. Res.* 18:171-175 (1996) or Lindsberg *et al. J. Neurosurg.* 82:269-277 (1995) in view of "art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients".

Mori *et al.*, Clark *et al.*, Bednar *et al.* and Lindsberg *et al.* are said to differ from the instant methods by not employing antibody fragments or humanized antibodies for treating human patients, but the Examiner urges such antibody modifications were standard procedures in increasing therapeutic efficacy and in treating human patients at the time the invention was made.

Mori *et al.*, Clark *et al.*, Bednar *et al.* and Lindsberg *et al.* are asserted to differ from the instant methods by not teaching the particular claimed time frames of 45 minutes to 5 hours and 15 minutes to about 20 hours. The Examiner states that the references teach treating within these time frames and further takes the view that providing bolus/continuous infusion would have been obvious.

With respect to claims 15-17 to articles of manufacture and kits, the Examiner alleges that it was well known convention in the art to place components in a kit for convenience and economy.

The Examiner concludes that one of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size.

While the rejected claims are not specified, Applicants believe that the rejection applies to claims 1-10 and 15-17.

Applicants have discussed Mori *et al.*, Clark *et al.* and Bednar *et al.* above with respect to the novelty rejections based on these references. As noted above, Bednar *et al.* is not prior art and Clark *et al.* taught away from the instantly claimed invention by suggesting that anti-CD18 antibodies would provide no clinical benefit in CNS ischemic injury where the arterial obstruction was not removed. Mori *et al.* evaluated the potential role of polymorphonuclear (PMN) leukocytes in the formation of microvascular perfusion defects or "no-reflow" early after middle cerebral artery (MCA) territory ischemia and reperfusion (column 2 on page 712). They conclude that "despite the increase in reflow, there was little change in the neurological score within 1 hour after reperfusion between control and IB4-treated groups" (last paragraph on page 717). Importantly, Mori *et al.* failed to evaluate the effect of an anti-CD18 antibody in a mammal where the arterial obstruction was not removed. Thus, Mori *et al.* fail to disclose or suggest that treatment with an anti-CD18 antibody will be clinically beneficial in patients where the arterial obstruction is not removed.

Like Mori *et al.*, Lindsberg *et al.* studied an anti-CD18 antibody in a reversible stroke model; rabbits were subjected to severe spinal cord ischemia by inflating the balloon of a catheter tip followed by 30 minutes of reperfusion at which time anti-CD18 antibody was administered (abstract and "Materials and Methods" section). Lindsberg *et al.* did not study the effect of an anti-CD18 antibody in a mammal where the arterial obstruction was not removed. Hence, this reference fails to teach or allude to the instantly claimed method wherein the arterial obstruction is not removed.

In summary, the prior art cited by the Examiner either: (a) does not teach a method of treating focal ischemic stroke caused by obstruction of a main cerebral artery where the arterial obstruction is not removed (Mori *et al.* and Lindsberg *et al.*) or (b) does refer to a method of treating ischemic injury where the arterial obstruction is not removed, but reports that anti-CD18 antibodies are not beneficial in this method (Clark *et al.*). Clearly the instantly claimed invention is nonobvious over the cited references.

With respect to claim 2, Applicants submit that the method claimed therein which increases both

cerebral blood flow and reduces infarct size in the mammal is not disclosed or alluded to in the references. As to claims 3-4, the cited references are concerned with administration of an intact antibody; there is no suggestion in these references to administer an antibody fragment (*e.g.* a $F(ab')_2$) with a presumably shorter half-life than an intact antibody. Accordingly, Applicants submit that claims 3-4 are independently patentable over the cited art. Moreover, Applicants submit that the dosing methods for treating a human patient (claims 6-8) and therapeutic windows for treating a human patient (claims 9-10) are nonobvious over the cited references. Finally, in relation to claims 15-17, Applicants submit that there is no motivation in the references to make the claimed article of manufacture and kit, since the method of treating a human as in claim 1 is not disclosed or suggested by the cited references.

Accordingly, Applicants respectfully request that the Section 103 rejection be reconsidered and withdrawn.

**§103 - Mori *et al.* or Clark *et al.* or Bednar *et al.* or Lindsberg *et al.* and Kim *et al.***

Claims 1-10 and 15-17 are rejected under 35 USC §103 as being unpatentable over Mori *et al. Stroke* 23(5):712-718 (1992) or Clark *et al. Stroke* 22(7):877-883 (1991) or Bednar *et al. Neurol. Res.* 18:171-175 (1996) or Lindsberg *et al. J. Neurosurg.* 82:269-277 (1995) and further in view of Kim *et al. J. Neurolog. Sciences*, 128:45-50 (1995).

Kim *et al.* is cited as allegedly providing evidence that CD11a and CD18 are upregulated in patients with ischemic stroke and transient ischemic attacks and that such adhesion molecules are involved in tissue injury in various cerebral vascular disorders including ischemic stroke. The Examiner takes the view that one of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke.

The primary references and the nonobvious nature of the instantly claimed method have been discussed in the previous section. Kim *et al.* fails to overcome the deficiencies of the above-discussed primary references in that it fails to provide a reasonable prediction that the instantly claimed method will be beneficial in the treatment of focal ischemic stroke where the arterial obstruction is not removed. Kim *et al.* looked at CD11a and CD18 in leukocytes from patients, but did not evaluate the effect of treating patients with anti-CD18 antibodies where the arterial obstruction was not removed. Given the observation of Clark *et al.* that anti-CD18 antibodies were <u>not</u> therapeutically beneficial for treating stroke where the arterial obstruction was not removed,

Applicants submit that the instantly claimed invention would not have been obvious from the cited art, prior to the discovery of the present application.

Accordingly, Applicants respectfully submit that the rejection should be reconsidered and withdrawn.

**§103 - Mori *et al.* or Clark *et al.* or Bednar *et al.* or Lindsberg *et al.* and Hildreth *et al.***

Claims 11-12 are rejected under 35 USC §103 as being unpatentable over Mori *et al. Stroke* 23(5):712-718 (1992) or Clark *et al. Stroke* 22(7):877-883 (1991) or Bednar *et al. Neurol. Res.* 18:171-175 (1996) or Lindsberg *et al. J. Neurosurg.* 82:269-277 (1995) and further in view of Hildreth *et al. Mol. Immunol.* 26(12):1155-1167 (1989) or Hildreth (WO90/15076). [If the Examiner still does not have a full copy of WO90/15076, Applicants will be happy to provide one.]

Applicants have shown above that Mori *et al.*, Clark *et al.*, Bednar *et al.* and Lindsberg *et al.* fail to disclose or suggest the invention as in claim 1 here. Since the two cited Hildreth references fail to specifically discuss the use of humanized H52 antibodies (optionally $F(ab')_2$) in the method as recited in claim 1, Applicants submit that this rejection should be reconsidered and withdrawn.

**§103 - Mori *et al.* or Clark *et al.* or Bednar *et al.* or Lindsberg *et al.* and Presta *et al.***

The rejection of claim 13 is moot in view of the nonprejudicial cancellation of this claim. Applicants request that this rejection be reconsidered and withdrawn.

Applicants believe that the amendments and comments here put this case in condition for allowance. Nevertheless, should the Examiner have any further comments or questions, he is invited to call Wendy Lee at (650) 225-1994 concerning these.

Respectfully submitted,

GENENTECH, INC.

Date: March 2, 1998

By: _____

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